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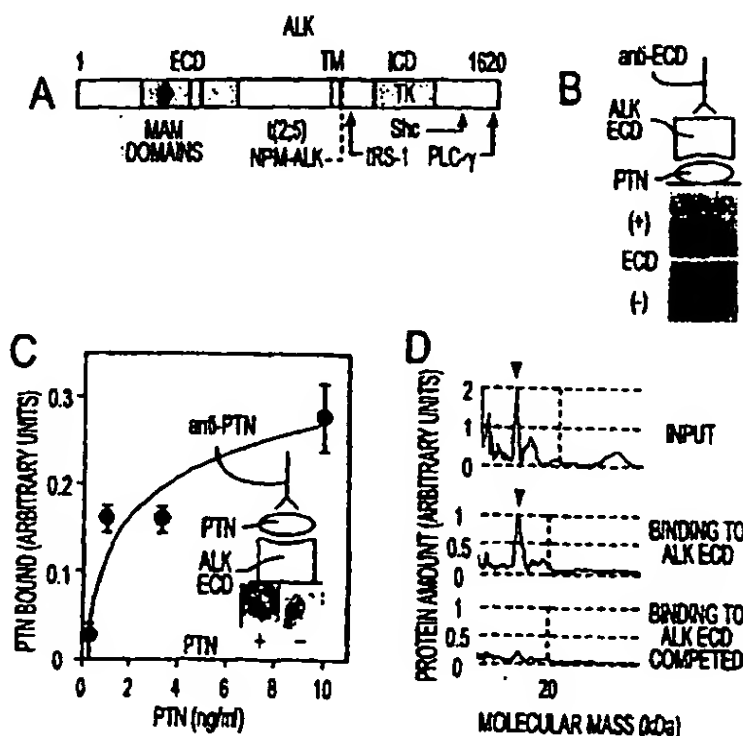
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6 March 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **PLEIOTROPHIN GROWTH FACTOR RECEPTOR FOR THE TREATMENT OF PROLIFERATIVE, VASCULAR AND NEUROLOGICAL DISORDERS**



(57) Abstract: This invention relates to the discovery that pleiotrophin binds to and activates a pleiotrophin-receptor which is responsible for the events associated with pleiotrophin activity including tumorigenesis, cell proliferation, and cell invasion. By interfering with that association, the cascade of events associated with pleiotrophin activity can be prevented or reversed. Further, by evaluating the effect of different compounds and conditions on the interaction, new drugs and treatments can be identified for use in preventing certain cancers and growth and developmental disorders.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/18938

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/475 C07K14/71 A61K38/18 A61K38/17 C07K16/22
C07K14/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, SEQUENCE SEARCH, EMBL, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENG KUNG ET AL: "Pleiotrophin signals increased tyrosine phosphorylation of beta-catenin through inactivation of the intrinsic catalytic activity of the receptor-type protein tyrosine phosphatase beta/zeta." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 6, 14 March 2000 (2000-03-14), pages 2603-2608, XP002222808 March 14, 2000 ISSN: 0027-8424 page 2604 -page 2606; figure 3 --- -/--	1-6, 10-12, 18-21,37



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

28 November 2002

Date of mailing of the international search report

19/12/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/18938

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAEDA NOBUAKI ET AL: "A receptor-like protein-tyrosine phosphatase PTPzeta/RPTPbeta binds a heparin-binding growth factor midkine: Involvement of arginine 78 of midkine in the high affinity binding to PTPzeta." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 18, 30 April 1999 (1999-04-30), pages 12474-12479, XP002222809 ISSN: 0021-9258 page 12475; figures 1,2	1-6,24, 25,29,30
X	MAEDA NOBUAKI ET AL: "6B4 proteoglycan/phosphacan, an extracellular variant of receptor-like protein-tyrosine phosphatase zeta/RPTP-beta, binds pleiotrophin/heparin-binding growth-associated molecule (HB-GAM)." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 35, 1996, pages 21446-21452, XP002222810 ISSN: 0021-9258 page 21448 -page 21449	1-6,37, 47,49-59
X	RAULO ERKKI ET AL: "Isolation of a neuronal cell surface receptor of heparin binding growth-associated molecule (HB-GAM): Identification as N-syndecan (syndecan-3)." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 269, no. 17, 1994, pages 12999-13004, XP002222811 ISSN: 0021-9258 page 13002 -page 13003; figures 3,6	1-6,37, 47,49-59
X	WO 00 20869 A (RAULAI DANIEL ;SOUTTOU BOUSSAD (FR); VIGNY MARC (FR); UNIV GEORGET) 13 April 2000 (2000-04-13) figure 1A; example I	31,32, 34-36
X	MATSUMOTO K ET AL: "A novel family of heparin-binding growth factors, pleiotrophin and midkine, is expressed in the developing rat cerebral cortex." DEVELOPMENTAL BRAIN RESEARCH, vol. 79, no. 2, 1994, pages 229-241, XP001120345 ISSN: 0165-3806 page 230, right-hand column -page 231, left-hand column page 233, left-hand column, paragraph 4 -page 235, left-hand column, paragraph 1	31,32,34

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INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/US 01/18938

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHANG NAN ET AL: "Domain structure of pleiotrophin required for transformation." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 19, 7 May 1999 (1999-05-07), pages 12959-12962, XP002222812 ISSN: 0021-9258 page 12960; figure 1	24-30
X	CAUGHEY DOROTHY J ET AL: "Fractionation of polyclonal antibodies to fragments of a neuroreceptor using three increasingly chaotropic solvents." JOURNAL OF CHROMATOGRAPHY B, vol. 728, no. 1, 14 May 1999 (1999-05-14), pages 49-57, XP002222813 ISSN: 0378-4347 page 52-54	10-12, 18-22, 37-41, 44
X	MORRIS STEPHAN W ET AL: "ALK, the chromosome 2 gene locus altered by the t(2;5) in non-Hodgkin's lymphoma, encodes a novel neural receptor tyrosine kinase that is highly related to leukocyte tyrosine kinase (LTK)." ONCOGENE, vol. 14, no. 18, 1997, pages 2175-2188, XP001119945 ISSN: 0950-9232 page 2185 -page 2186	10-12, 18-21, 37, 38, 44
X	IWAHARA TOSHINORI ET AL: "Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system." ONCOGENE, vol. 14, no. 4, 1997, pages 439-449, XP009001671 ISSN: 0950-9232 page 442 page 448, left-hand column, paragraph 2	10-12, 18-21, 37, 38, 44
X	PULFORD KAREN ET AL: "Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (NPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1." BLOOD, vol. 89, no. 4, 1997, pages 1394-1404, XP002222814 ISSN: 0006-4971 page 1395 page 1397, left-hand column, paragraph 3 -page 1398, left-hand column, paragraph 3; figure 2	10-12, 18-21, 37, 38, 44-46

INTERNATIONAL SEARCH REPORT

Int

al Application No

PCT/US 01/18938

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>AIGNER A ET AL: "Identification of a receptor for the growth factor pleiotrophin, its signal transduction and potential role in cancer." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 40, March 1999 (1999-03), page 732 XP001119959 90th Annual Meeting of the American Association for Cancer Research; Philadelphia, Pennsylvania, USA; April 10-14, 1999, March, 1999 ISSN: 0197-016X abstract</p>	
✓ P,X	<p>STOICA GERALD E ET AL: "Identification of anaplastic lymphoma kinase as a receptor for the growth factor pleiotrophin." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 20, 18 May 2001 (2001-05-18), pages 16772-16779, XP002222815 ISSN: 0021-9258 the whole document</p>	1-68

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INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 01/18938

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 60-68 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Initial International Application No

PCT/US 01/18938

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0020869	A	13-04-2000	CA 2346406 A1	13-04-2000
			EP 1121598 A1	08-08-2001
			JP 2002526777 T	20-08-2002
			WO 0020869 A1	13-04-2000

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003, Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) **\$180.00**

Complete if Known

Application Number	09/880,097
Filing Date	June 14, 2001
First Named Inventor	Anton Wellstein
Examiner Name	Nichols, Christopher J
Art Unit	1647
Attorney Docket No.	544582000200

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number

03-1952

Deposit Account Name

Morrison & Foerster LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) (\$)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims - 20 = x =
Independent Claims - 3 = x =
Multiple Dependent =

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) **[Text].00**

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	180.00
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$) **180.00**

SUBMITTED BY

(Complete (if applicable))

Name (Print/Type)	James Remerick	Registration No. (Attorney/Agent)	36,902	Telephone	703-760-7728
Signature		Date	July 20, 2004		

VA-72065

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